Carnrick Laboratories—Cont.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Hydrocet® Capsules (Hydrocodone bitartrate and acetaminophen) are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, Hydrocet® Capsules (hydrocodone bitartrate and acetaminophen) should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Hydrocet® Capsules (hydrocodone bitartrate and acetaminophen) are used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocet® Capsules (hydrocodone bitartrate and acetaminophen) may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Hydrocet® Capsules (hydrocodone bitartrate and acetaminophen) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of Hydrocet® Capsules (hydrocodone bitartrate and acetaminophin) may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritis.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocet® Capsules (hydrocodone bitartrate and acetaminophen) are classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when Hydrocet® Capsules (hydrocodone bitartrate and acetaminophen) are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious ovedose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis) extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage; dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydro... and acetaminophen is a potentially lethal polydru... dose, and consultation with a regional poison contro... is recommended.

Immediate treatment includes support of cardiores... function and measures to reduce drug absorption. V... should be induced mechanically, or with syrup of ip... the patient is alert (adequate pharyngeal and larynge... flexes). Oral activated charcoal (1g/kg) should follow... emptying. The first dose should be accompanied by an... priate cathartic. If repeated doses are used, the cath... might be included with alternate doses as required. Hy... sion is usually hypovolemic and should respond to ... Vasopressors and other supportive measures should b... ployed as indicated. A cuffed endo-tracheal tube shou... inserted before gastric lavage of the unconscious patient... when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining ... quate pulmonary ventilation. In severe cases of intoxi... peritoneal dialysis, or preferably hemodialysis may b... sidered. if hypoprothrombinemia occurs due to acetam... phen overdose, vitamin K should be administered pa... nously.

Naloxone, a narcotic antagonist, can reverse respir... depression and coma associated with opioid overdose. N... one hydrochloride 0.4 mg to 2 mg is given parenterally; ... the duration of action of hydrocodone may exceed that ... naloxone, the patient should be kept under continuous ... veillance and repeated doses of the antagonist should b... ministered as needed to maintain adequate respiratio... narcotic antagonist should not be administered in th... sence of clinically significant respiratory or cardiovas... depression.

If the dose of acetaminophen may have exceeded 140 m... acetylcysteine should be administered as early as poss... Serum acetaminophen levels should be obtained, since ... four or more hours following ingestion help predict occ... nophen toxicity. Do not await acetaminophen assay re... before initiating treatment. Hepatic enzymes should ... obtained initially, and repeated at 24-hour intervals. ... Methemoglobinemia over 30% should be treated ... methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain ... response of the patient. However, it should be kept in ... that tolerance to hydrocodone can develop with conti... use and that the incidence of untoward effects is dose ... lated.

The usual adult dosage is one or two capsules every ... six hours as needed for pain. The total daily dosage s... not exceed 8 capsules.

HOW SUPPLIED

Blue and white, opaque capsules imprinted with the le... "C" and 8657.

Each capsule contains Hydrocodone Bitartrate*, USP ... *(WARNING: MAY BE HABIT FORMING.) and Acetam... phen, USP 500 mg. Keep in tight, light resistant contai...

Supplied in bottles of 100 capsules NDC 0086-0067-10.

Store at controlled room temperature, 15°-30°C (59°-...

The most recent revision of this labeling is February ...

Manufactured for:

Carnrick Laboratories, Inc.

Shown in Product Identification Guide, page 38...

MIDRIN®

[*mid'rin*]

CAUTION

Federal law prohibits dispensing without prescription.

DESCRIPTION

Each red capsule with pink band contains Isometh... Mucate 65 mg., Dichloralphenazone 100 mg., and Acet... nophen 325 mg.

Isometheptene Mucate is a white crystalline powder ha... a characteristic aromatic odor and bitter taste. It is an ... urated aliphatic amine with sympathomimetic prope...

Dichloralphenazone is a white, microcrystalline pow... with slight odor and tastes saline at first, becoming acr... is a mild sedative.

Acetaminophen, a non-salicylate, occurs as a white, odo... crystalline powder possessing a slightly bitter taste.

Midrin capsules contain FD&C Yellow No. 6 as a ... additive.

ACTIONS

Isometheptene Mucate, a sympathomimetic amine, a... constricting dilated cranial and cerebral arterioles ... reducing the stimuli that lead to vascular headache... chloralphenazone, a mild sedative, reduces the pa... emotional reaction to the pain of both vascular and ... headaches. Acetaminophen raises the threshold to p...

smooth, thus exerting an analgesic effect against all types of headaches.

INDICATIONS

For relief of tension and vascular headaches.*

*Based on a review of this drug (isometheptene mucate) by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the other indication as "possibly" effective in the treatment of migraine headache. Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS

Midrin is contraindicated in glaucoma and/or severe cases of renal disease, hypertension, organic heart disease, hepatic disease and in those patients who are on monoamine-oxidase (MAO) inhibitor therapy.

PRECAUTIONS

Caution should be observed in hypertension, peripheral vascular disease and after recent cardiovascular attacks.

ADVERSE REACTIONS

Transient dizziness and skin rash may appear in hypersensitive patients. This can usually be eliminated by reducing the dose.

DOSAGE AND ADMINISTRATION

FOR RELIEF OF MIGRAINE HEADACHE: The usual adult dosage is two capsules at once, followed by one capsule every hour until relieved, up to 5 capsules within a twelve hour period.

FOR RELIEF OF TENSION HEADACHE: The usual adult dosage is one or two capsules every four hours up to 8 capsules a day.

HOW SUPPLIED

Red capsules imprinted with pink band, the letter "C" and 86120. Bottles of 50 capsules, NDC 0086-0120-05. Bottles of 100 capsules, NDC 0086-0120-10. Store at controlled room temperature 15–30°C (59–86°F) in a dry place.

The most recent revision of this labeling is Nov. 1988.

Manufactured for Carnrick Laboratories, Inc.

Shown in Product Identification Guide, page 308

MOTOFEN®

Tablets

(difenoxin hydrochloride with atropine sulfate)

antidiarrheal

DESCRIPTION

Each five-sided dye free MOTOFEN tablet contains:

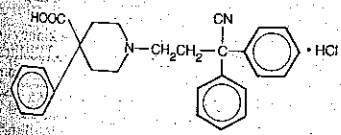
Difenoxin (as the hydrochloride) ..... 1.0 mg

Warning—May be habit forming.

Atropine sulfate ..... 0.025 mg

Difenoxin hydrochloride, 1-(3-cyano-3,3-diphenylpropyl)-4-phenyl-4-piperidinecarboxylic acid monohydrochloride, is an orally administered antidiarrheal agent which is chemically related to the narcotic meperidine.

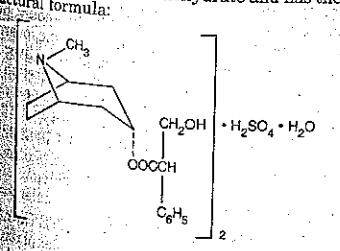
The structural formula is:



Difenoxin Hydrochloride

Atropine sulfate is present to discourage deliberate overdosage.

Atropine sulfate, an anticholinergic, is endo (±)-α-(hydroxymethyl) benzeneacetic acid 8-methyl-8-azabicyclo[3.2.1] oct-3-yl ester sulfate (2:1) (salt) monohydrate and has the following structural formula:



Atropine Sulfate

Inactive ingredients: calcium stearate, cellulose, lactose, corn starch.

CLINICAL PHARMACOLOGY

Animal studies have shown that difenoxin hydrochloride manifests its antidiarrheal effect by slowing intestinal motility. The mechanism of action is by a local effect on the gastrointestinal wall.

Difenoxin is the principal active metabolite of diphenoxylate.

Following oral administration of MOTOFEN, difenoxin is rapidly and extensively absorbed. Mean peak plasma levels of approximately 160 ng/mL occurred within 40 to 60 minutes in most patients following an oral dose of 2mg. Plasma levels decline to less than 10% of their peak values within 24 hours and to less than 1% of their peak values within 72 hours. This decline parallels the appearance of difenoxin and its metabolites in the urine. Difenoxin is metabolized to an inactive hydroxylated metabolite. Both the drug and its metabolites are excreted, mainly as conjugates, in urine and feces.

INDICATIONS AND USAGE

MOTOFEN (difenoxin hydrochloride with atropine sulfate) is indicated as adjunctive therapy in the management of acute nonspecific diarrhea and acute exacerbations of chronic functional diarrhea.

CONTRAINDICATIONS

MOTOFEN is contraindicated in patients with diarrhea associated with organisms that penetrate the intestinal mucosa (toxigenic *E. coli, Salmonella* species, *Shigella*) and pseudomembranous colitis associated with broad spectrum antibiotics. Antiperistaltic agents should not be used in these conditions because they may prolong and/or worsen diarrhea.

MOTOFEN is *contraindicated in children under 2 years of age* because of the decreased margin of safety of drugs in this class in younger age groups.

MOTOFEN is contraindicated in patients with a known hypersensitivity to difenoxin, atropine, or any of the inactive ingredients, and in patients who are jaundiced.

WARNINGS

MOTOFEN IS *NOT* AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO. MOTOFEN IS NOT RECOMMENDED FOR CHILDREN UNDER 2 YEARS OF AGE. OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH (SEE *OVERDOSAGE*). THEREFORE, KEEP THIS MEDICATION OUT OF THE REACH OF CHILDREN.

FLUID AND ELECTROLYTE BALANCE—THE USE OF MOTOFEN DOES NOT PRECLUDE THE ADMINISTRATION OF APPROPRIATE FLUID AND ELECTROLYTE THERAPY. DEHYDRATION, PARTICULARLY IN CHILDREN, MAY FURTHER INFLUENCE THE VARIABILITY OF RESPONSE TO MOTOFEN AND MAY PREDISPOSE TO DELAYED DIFENOXIN INTOXICATION. DRUG-INDUCED INHIBITION OF PERISTALSIS MAY RESULT IN FLUID RETENTION IN THE COLON, AND THIS MAY FURTHER AGGRAVATE DEHYDRATION AND ELECTROLYTE IMBALANCE.

IF SEVERE DEHYDRATION OR ELECTROLYTE IMBALANCE IS MANIFESTED, MOTOFEN SHOULD BE WITHHELD UNTIL APPROPRIATE CORRECTIVE THERAPY HAS BEEN INITIATED.

Ulcerative Colitis—In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or delay intestinal transit time have been reported to induce toxic megacolon. Consequently, patients with acute ulcerative colitis should be carefully observed and MOTOFEN therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop.

Liver and Kidney Disease—MOTOFEN (difenoxin hydrochloride with atropine sulfate) should be used with extreme caution in patients with advanced hepatorenal disease and in all patients with abnormal liver function tests since hepatic coma may be precipitated.

Atropine—A subtherapeutic dose of atropine has been added to difenoxin hydrochloride to discourage deliberate overdosage. Usage of MOTOFEN in recommended doses is not likely to cause prominent anticholinergic side effects, but MOTOFEN should be avoided in patients in whom anticholinergic drugs are contraindicated. The warnings and precautions for use of anticholinergic agents should be observed. In children, signs of atropinism may occur even with recommended doses of MOTOFEN, particularly in patients with Down's Syndrome.

PRECAUTIONS

Information for Patients

CAUTION PATIENTS TO ADHERE STRICTLY TO RECOMMENDED DOSAGE SCHEDULES. THE MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN SINCE ACCIDENTAL OVERDOSAGE MAY RESULT IN SEVERE, EVEN FATAL, RESPIRATORY DEPRESSION.

MOTOFEN may produce drowsiness or dizziness. The patient should be cautioned regarding activities requiring mental alertness, such as driving or operating dangerous machinery.

Drug Interactions

Since the chemical structure of difenoxin hydrochloride is similar to meperidine hydrochloride, the concurrent use of MOTOFEN with monoamine oxidase inhibitors may, in theory, precipitate a hypertensive crisis.

MOTOFEN may potentiate the action of barbiturates, tranquilizers, narcotics, and alcohol. When these medications are used concomitantly with MOTOFEN, the patient should be closely monitored.

Diphenoxylate hydrochloride, from which the principal active metabolite difenoxin is derived, was found to inhibit the hepatic microsomal enzyme system at a dose of 2 mg/kg/day in studies conducted with male rats. Therefore, difenoxin has the potential to prolong the biological half-lives of drugs for which the rate of elimination is dependent on the microsomal drug metabolizing enzyme system.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenesis was found in a long-term study of difenoxin hydrochloride/atropine in the rat. In this 104 week study, rats received dietary doses of 0, 1.25, 2.5, or 5 mg/kg/day difenoxin/atropine (20:1 ratio).

No experiments have been conducted to determine the mutagenic potential of MOTOFEN. MOTOFEN did not significantly impair fertility in rats.

Pregnancy/Teratogenic Effects

Pregnancy Category C. Reproduction studies in rats and rabbits with doses at 31 and 61 times the human therapeutic dose respectively, on a mg/kg basis, demonstrated no evidence of teratogenesis due to MOTOFEN (difenoxin hydrochloride with atropine sulfate).

Pregnant rats receiving oral doses of difenoxin hydrochloride/atropine 20 times the maximum human dose had an increase in delivery time as well as a significant increase in the percent of stillbirths.

Neonatal survival in rats was also reduced with most deaths occurring within four days of delivery.

There are no well controlled studies in pregnant women. MOTOFEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants from MOTOFEN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

SAFETY AND EFFECTIVENESS IN CHILDREN BELOW THE AGE OF 12 HAVE NOT BEEN ESTABLISHED. MOTOFEN IS CONTRAINDICATED IN CHILDREN UNDER 2 YEARS OF AGE. See OVERDOSAGE section for information on hazards from accidental poisoning in children.

ADVERSE REACTIONS

In view of the small amount of atropine present (0.025 mg/tablet), effects such as dryness of the skin and mucous membranes, flushing, hyperthermia, tachycardia and urinary retention are very unlikely to occur, except perhaps in children.

Many of the adverse effects reported during clinical investigation of MOTOFEN are difficult to distinguish from symptoms associated with the diarrheal syndrome. However, the following events were reported at the stated frequencies:

Gastrointestinal: Nausea, 1 in 15 patients; vomiting, 1 in 30 patients; dry mouth, 1 in 30 patients; epigastric distress, 1 in 100 patients; and constipation, 1 in 300 patients.

Central Nervous System: Dizziness and light-headedness, 1 in 20 patients; drowsiness, 1 in 25 patients; and headache, 1 in 40 patients; tiredness, nervousness, insomnia and confusion ranged from 1 in 200 to 1 in 600 patients.

Other less frequent reactions: Burning eyes and blurred vision occurred in a few cases.

The following adverse reactions have been reported in patients receiving chemically-related drugs: numbness of extremities, euphoria, depression, sedation, anaphylaxis, angioneurotic edema, urticaria, swelling of the gums, pruritus, toxic megacolon, paralytic ileus, pancreatitis, and anorexia.

THIS MEDICATION SHOULD BE KEPT IN A CHILD-RESISTANT CONTAINER AND OUT OF THE REACH OF CHILDREN SINCE AN OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH.

DRUG ABUSE AND DEPENDENCE

MOTOFEN (difenoxin hydrochloride with atropine sulfate) tablets are a Schedule IV controlled substance.

Addiction to (dependence on) difenoxin hydrochloride is theoretically possible at high dosage. Therefore, the recommended dosage should not be exceeded. Because of the structural and pharmacological similarities of difenoxin hydrochloride to drugs with a definite addiction potential, MOTOFEN should be administered with considerable cau-

Continued on next page